

Claim 5, line 2, delete "linked" and insert therefor  
--joined--.

REMARKS

The Office Action and the cited and applied reference have been carefully studied. No claims are allowed. Claims 1-14 and 19 presently appear in this application with claims 7-13 withdrawn from consideration at this stage as being drawn to a non-elected species. The present claims define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The title of the invention is held to be not descriptive and is replaced with a new title as required.

The disclosure has been objected to because of informalities. Appropriate correction to the specification is made, thereby obviating this objection.

Claims 1-16, 14 and 19 have been rejected under 35 USC §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

The examiner finds claim 2 to be indefinite as it is not clear to the examiner how antibody light chains can be capable of retaining binding capacity in the absence of a heavy chain, or vice versa. It is clear, however, that when sequence (a) is an antibody light chain associated with an antibody heavy chain, the antibody would have binding capability. Thus, a hybrid protein heterodimer of the present invention could have two identical antibody sequence (a) for a valence of 2 or two different antibody sequences (a) for a bifunctional "antibody". When sequence (a) of one coexpressed amino acid sequence is an

antibody light chain, and the sequence (a) of the other coexpressed amino acid sequence forming the dimer is an antibody heavy chain, then the association of these two different sequences (a) would provide binding capability. In this situation, each sequence (a) only has a single chain, either light or heavy, of the antibody.

In claims 4 and 5, applicants are merely intending to indicate orientation of sequence (a) relative to sequence (b).

The examiner finds claim 14 indefinite because it is not clear how "one or more covalent bonds" are added. Applicants respectfully direct the examiner's attention to the paragraph bridging pages 7 and 8 of the present specification, where it is disclosed that covalent bonds between the two subunits (b) are added to enhance the stability of the resulting hybrid protein, such as by adding one or more non-native interchain disulfide bonds at suitable sites based on the known structure of heterodimeric hormones.

The remaining portions of this rejection are obviated by the amendment to the claims. Accordingly, reconsideration and withdrawal of the rejection are, therefore, respectfully requested.

Claims 1-5, 14 and 19 have been rejected under 35 USC §103(a) as being unpatentable over Boime, U.S. Patent 5,705,478. The examiner states that Boime discloses single-chain proteins which comprise two individual subunits of a glycoprotein hormone, where the glycoprotein hormones LH, CG, FSH and TSH are heterodimeric proteinaceous hormones. At col. 4, Boime is said to disclose that the protein may comprise an  $\alpha$  and a  $\beta$  subunit, optionally linked with a linker moiety between the two,

in a head-to-head, tail-to-tail or head-to-tail configuration. At cols. 12-13, Boime is further said by the examiner to disclose that the linker moiety may itself have biological activity, the numerous species listed at col. 13 being "ligands" within the meaning in the instant application, e.g., various cytokines and interleukins. Also at col. 13, beginning at line 15, the examiner holds that Boime discloses the inclusion of a proteolytic cleavage site within the linker to allow release of the drug from the fusion protein. DNA encoding the hybrid protein, vectors, host cells and recombinant production of protein are indicated as being disclosed at cols. 13-15. The examiner asserts that Boime differs from the instant specification in that the invention therein is directed to single-chain pseudodimers, which would fold back upon themselves, rather than the proposal that the individual chains would associate with a second chain to form a heterodimer. However, the examiner takes the position that a construct encoding, as suggested by Boime, an  $\alpha$  and a  $\beta$  glycoprotein hormone subunit separated by a linker moiety, such as an interleukin, would result in the production of a hybrid protein as claimed, given the ability of the  $\alpha$  and  $\beta$  subunits to dimerize. While the examiner admits that the predominant resultant protein might well be a pseudodimeric protein as intended by Boime, the examiner asserts that the ordinary artisan would immediately realize that dimeric and multimeric proteins would also form, due to the interaction of (for instance) the  $\alpha$  portion of one protein and the  $\beta$  portion of another. Therefore, the examiner concludes that the invention

is *prima facie* obvious over the disclosure of Boime. This rejection is respectfully traversed.

The examiner's position that the  $\alpha$  and  $\beta$  glycoprotein hormone subunits, which are separated by a linker moiety, such as interleukin, would result in the production of the presently claimed hybrid protein, given the ability of the  $\alpha$  and  $\beta$  subunits to dimerize, does not make the present invention *prima facie* obvious. It appears that according to the examiner, based on Boime's description of alpha-beta fusion proteins, the following dimer can be formed from dimerization of Boime's single-chain glycoprotein hormones:

alpha -- linker moiety/fused protein -- beta

beta -- linker moiety/fused protein -- alpha

However, even if one of ordinary skill in the art were to recognize that Boime's single-chain glycoprotein hormones could dimerize (which is pure speculation), this same person of ordinary skill in the art would further recognize that the conformation of the linker moiety/fused protein in the above dimer would be quite different from its conformation in the "pseudodimeric" single-chain glycoprotein hormone as intended by Boime. If the glycoprotein hormone is designed to be a single chain, in which the  $\alpha$  and  $\beta$  glycoprotein hormone subunits fold back upon themselves to form a "pseudoheterodimer", such as

alpha  
    > linker moiety/fused protein  
beta

where the linker moiety/fused protein would have biological activity, i.e., receptor ligand binding, then it would be predicted and expected by one of ordinary skill in the art that such an active conformation of the linker moiety/fused protein

in the "pseudoheterodimer" would be disrupted when the alpha and beta subunits are not folded upon themselves, but are instead associated with corresponding alpha and beta subunits from another single-chain glycoprotein hormone to form a dimer.

In the present invention, each of the recited sequences (a) in the hybrid protein dimer are not sandwiched between an alpha and a beta subunit in a dimer form as would be in Boime's single-chain glycoprotein hormone with the steric and conformational constraints associated with such a dimerization. As presently recited in claim 1, each of the sequences (a) listed therein in Markush format retain ligand-receptor binding capability. This cannot be said for the linker moiety/fused protein in the pseudoheterodimer of Boime, which is taken by the examiner as being capable of forming a heterodimer as shown above. Accordingly, Boime cannot make obvious the presently claimed invention.

Furthermore, if one of ordinary skill in the art were to recognize that dimers and multimers may form from Boime's single-chain glycoprotein hormones, then it would be apparent to this same person that there is no way to predetermine the ratio of pseudoheterodimers, dimers and higher order complexes such as:

|                            |                            |
|----------------------------|----------------------------|
| alpha--fused protein--beta | alpha--fused protein--beta |
| alpha--fused protein--beta |                            |

Consequently, a uniform dimeric product cannot be achieved with Boime's single-chain glycoprotein hormone.

Reconsideration and withdrawal of the rejection are, therefore, respectfully requested.

The prior art documents cited but not relied upon have been noted, along with the implication that such documents are

not deemed sufficiently pertinent by the PTO to warrant their application against applicants' claims.

In view of the above, the claims comply with 35 USC §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.  
Attorneys for Applicant(s)

By 

Allen C. Yun  
Registration No. 37,971

ACY:rd  
Telephone No.: (202) 628-5197  
Facsimile No.: (202) 737-3528  
itt3\acy\campb2a.amd